Continuous manufacturing of delta mannitol by cospray drying with PVP

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Abstract

Mannitol is a frequently used diluent in the production of tablets due to its non-hygroscopic character and low drug interaction potential. Although the δ-polymorph of mannitol has superior tabletability in comparison to α- and β-mannitol, the latter are most commonly used because large-scale production of δ-mannitol is difficult. Therefore, a continuous method for production of δ-mannitol was developed in the current study. Spray drying an aqueous solution of mannitol and PVP in a ratio of 4:1 resulted in formation of δ-mannitol. The tabletability of a physical mixture of spray dried δ-mannitol with PVP (5%) and paracetamol (75%) was clearly superior to the tabletability of physical mixtures consisting of spray dried α- and β-mannitol with PVP (5%) and paracetamol (75%) which confirmed the excellent tableting properties of the δ-polymorph. In addition, a coprocessing method was applied to coat paracetamol crystals with δ-mannitol and PVP. The tabletability of the resulting coprocessed particles consisting of 5% PVP, 20% δ-mannitol and 75% paracetamol reached a maximal tensile strength of 2.1 MPa at a main compression pressure of 260 MPa. Moreover the friability of tablets compressed at 184 MPa was only 0.5%. This was attributed to the excellent compression properties of δ-mannitol and the coating of paracetamol crystals with δ-mannitol and PVP during coprocessing.

KEYWORDS: Delta mannitol, Spray drying, Coprocessing, Particle coating, Direct compression, Paracetamol, Tabletability, Continuous production.

List of abbreviations

d_{50}	Median particle size
ffc	Flowability index
MCP	Main compression pressure
MDSC	Modulated differential scanning calorimetry
PC	Principal component
PCA	Principal component analysis
PVP	Polyvinylpyrrolidone
SEM	Scanning electron microscopy
To	Outlet temperature
TS	Tensile strength
XRD	X-ray diffraction

1. Introduction

Tablets are the most commonly used dosage form, accounting for 70-80% of all pharmaceutical preparations, due to their ease of manufacturing, accurate dosing and high patient compliance [1, 2].

Mannitol is an acyclic sugar often used as tablet diluent in the neutraceutical and pharmaceutical industry [3]. The major advantages of mannitol over other excipients are its non-hygroscopic character, which makes it an excipient of choice for moisture sensitive drugs, and its low drug interaction potential [4, 5, 6]. Mannitol is also frequently used in chewable and orodispersible tablets due to its sweetness, cooling mouth sensation, high solubility and fast disintegration in water [3, 4, 6]. Especially with pediatric and geriatric patients, rapidly disintegrating and dispersing tablets can add to the patients' compliance as it overcomes swallowing problems. Additionally, mannitol is used as a bulking agent in lyophilizates due to its ability to form solid, elegant cakes in the vials [4, 7].

Three polymorphs, α-, β- and δ-mannitol, and mannitol hemi-hydrate, a pseudo-polymorphic form formed during freeze-drying, have been described in literature [8]. Burger et al. evaluated the compaction properties of these three polymorphs since the crystallographic and thermodynamic properties of polymorphs vary which can affect their compaction behavior [8]. They reported on superior compressibility and tabletability of the δ-polymorph in comparison to the α- and β-polymorphs of mannitol. More recently, Wagner et al. confirmed this result as they found an improved tabletability of δ-mannitol granules after roller compaction [3].

Several crystallization reactions are reported for the production of δ-mannitol [8, 9, 10, 11]. However, reproducible and scalable production of δ-mannitol by crystallization is difficult [8]. δ-mannitol was also obtained during cospray drying of aqueous solutions of mannitol and trypsin in different ratios [12]. However, a coprocessed excipient including a protease is not preferred. As a result, commercially available mannitol grades consist almost exclusively of α- or β-mannitol or a mixture thereof. Therefore, it was the first aim to develop a continuous manufacturing method for the production of δ-mannitol via spray drying. Aqueous solutions of mannitol and polyvinylpyrrolidone (PVP) were spray dried at two outlet drying temperatures and the polymorphic content and tabletability of these spray dried samples were evaluated.

The second part of the study evaluated if coprocessing of paracetamol with δ-mannitol and PVP could overcome the poor tabletability of paracetamol in a single processing step. Coprocessing of excipients is widely practiced for the production of

directly compressible excipients: e.g. Cellactose® (microcrystalline cellulose and lactose), Ludipress® (lactose, PVP and crospovidone), StarLac® (lactose and maize starch), Avicel® CE (microcrystalline cellulose and guar gum) [1]. Cospray drying of excipients and active pharmaceutical ingredients has also been successfully applied to generate agglomerates with a unique particle size and shape and physicochemical properties [13]. In the current study, a coprocessing method recently described by Vanhoorne et al. was applied for the production of a coprocessed mixture consisting of 5% PVP, 20% δ-mannitol, and 75% paracetamol [14]. The morphology, solid state and particle size distribution of the coprocessed sample was evaluated and its compression properties were compared to a physical mixture.

2. Materials and methods

2.1. Materials

α-mannitol (Pearlitol 200) and β-mannitol (C*PharmMannidex) were kindly donated by Cargill (Vilvoorde, Belgium). δ-mannitol (Parteck Delta) was kindly donated by Merck (Darmstadt, Germany). These mannitol samples were used as reference material. β-mannitol was used for the preparation of the spray dried solutions. Paracetamol (semi-fine) was received from Mallinckrodt Chemical (Hazelwood, USA). Magnesium stearate and silicon dioxide (Fagron, Waregem, Belgium) were used as lubricant and glidant, respectively. PVP (Kollidon 30) and crospovidon (Kollidon CR) were received from BASF (Burgbernheim, Germany). Miglyol 812 (Cremer Oleo, Witten, Germany) with 0.2% polysorbate 80 (Fagron, Waregem, Belgium) was used as dispersant for laser diffraction measurements.

2.2. Methods

2.2.1. Spray drying and coprocessing

In preliminary spray drying experiments, an 18% w/w aqueous solution of mannitol and PVP (ratio mannitol:PVP: 4:1) and an 18% w/w aqueous solution of pure mannitol were spray dried (F1 and F2, respectively) on a lab-scale spray dryer (B290, Büchi Labortechnik, Flawil, Switzerland) equipped with a two-fluid nozzle (nozzle orifice 1.4 mm). The spray dried samples were collected after the cyclone. The solutions were spray dried at a constant feed rate of 16 g/min and an

atomization pressure of 50%. The inlet and outlet drying air temperature were 220 and 80 °C, respectively.

In the main spray drying experiments, 18% w/w aqueous solutions of mannitol and PVP (mannitol:PVP ratios of 9:1 and 4:1) and an 18% w/w aqueous solution of pure mannitol were spray dried on a pilot-scale spray dryer (Mobile Minor, GEA Niro, Copenhagen, Denmark) equipped with a two-fluid nozzle (nozzle orifice 2.0 mm). The solutions were transferred to the spray dryer by a peristaltic pump (520U, Watson Marlow, Cornwall, UK) with marprene tubing (inside diameter 4.8 mm). The spray dryer was operated in co-current mode. The dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and 60° conical base. The solutions were spray dried at a constant feed rate of 45 g/min and an atomizing air pressure of 1 bar. The inlet drying air temperature was varied between 170 and 220 °C, resulting in outlet temperatures of 60 and 80 °C, respectively.

An overview of the spray dried solutions (F1-3) on the lab-scale and pilot-scale spray dryers and the composition of the resulting solid samples is given in Table 1. The yield (%) of the spray drying process was defined as the weight fraction of the material recovered from the collecting reservoir after spray drying in relation to the amount of mannitol and PVP originally contained in the atomized liquid feed.

In a second part of the study, paracetamol crystals were coated with mannitol and with mannitol and PVP via a coprocessing method proposed by Vanhoorne et al. in order to improve the tabletability of paracetamol crystals [Vanhoorne]. A detailed description of the method and schematic setup was given by Vanhoorne et al. [14]. Hence, 18% w/w aqueous solutions of pure mannitol and of mannitol and PVP (mannitol:PVP ratio: 4:1) were fed to the fountain two-fluid nozzle (nozzle orifice 2.6 mm) of a production-scale spray dryer (type 6.3-SD, GEA Niro, Copenhagen, Denmark) by a peristaltic pump (520U, Watson Marlow, Cornwall, UK) and marprene tubing (inside diameter 4.8 mm). The spray dryer operated in counter-current mode. The dimensions of the spray dryer were 2.0 m cylindrical height with a diameter of 3.5 m and 60° conical base. The spray dried powder was collected in a reservoir under the drying chamber. The solutions were spray dried according to the following parameters: feed rate: 100 g/min, inlet drying air temperature: 240 °C, outlet drying air temperature: 112 °C, atomizing air pressure 0.5 bar. Paracetamol crystals were preblended with 0.05% silicon dioxide and introduced during the spray drying process at a feed rate of 48 g/min into the cone of the spray dryer via an in-house designed setup described by Vanhoorne et al. [14]. Using this setup, the paracetamol crystals were directly injected into the spray of atomized drops in the drying chamber of the spray dryer. The composition of the

spray dried solutions and final composition of the coprocessed powders (F4 and F5) is included in Table 1.

2.2.2. Preparation of physical mixtures

Physical mixtures (PM1-4) were prepared in a tumbling blender (Turbula mixer type T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) for 10 min at 49 rpm to evaluate the influence of PVP and the added value of coprocessing via spray drying on tabletability. An overview of the prepared physical mixtures is listed in Table 2.

2.2.3. Tableting

The spray dried and coprocessed powders and physical mixtures were blended (Turbula mixer type T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) for 5 min at 49 rpm with 5% crospovidon® and 0.5% magnesium stearate prior tableting.

Tablets (500 mg ± 10 mg) of the spray dried and coprocessed powders (F1-5) and physical mixtures (PM1-4) were compressed on a rotary tablet press (Modul™ P, GEA Courtoy, Halle, Belgium) equipped with a single round concave Euro B punch of 12 mm diameter at a tableting speed of 5 rpm. The tablets were compressed at 6 different compaction pressures: 34 (± 8), 61 (±9), 100 (±11), 143 (±10), 184 (±5) and 229 (±9) MPa.

2.2.4. Material characterization

2.2.4.1. Morphology

The powders were examined by scanning electron microscopy (SEM) (JEOL JSM-5600-LV, JEOL Ltd., Zaventem, Belgium) after sputtering with a platinum coating using the JEOL JFC 1300 Autofine Coater (JEOL, Zaventem, Belgium) to improve the electron conductivity of the samples.

2.2.4.2. Karl Fischer titration

To determine the residual moisture content, Karl Fischer titrations (Mettler DL35, Mettler Toledo, Zaventem, Belgium) were performed (n=3) on the powder samples immediately after production. Powder (100–200 mg) was added to an airtight beaker containing absolute dry methanol (Biosolve, Valkenswaard, the Netherlands). Titration of the samples was performed using Karl Fischer reagent (Hydranal_Composite 2, Sigma–Aldrich, Munich, Germany). The mixture was stirred for 5 min before actual titration.

2.2.4.3. Particle size analysis

The particle size distribution of the paracetamol starting material, spray dried and coprocessed powders was measured in triplicate by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK) and the average particle size distribution was calculated via the Mastersizer 2000 software. The wet dispersion technique was applied using the 300RF lens (Malvern Instruments, Worcestershire, UK). The powders were dispersed in a solution of 0.2% Tween 80 in Miglyol 812 and subsequently vortexed and sonicated in order to eliminate agglomerates. The results are expressed as volume diameters.

2.2.4.4. Ring shear testing

The flowability expressed as the flowability index (ffc) of the powders was measured in triplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany). The powders were tested using a preshear of 1000 Pa at three consolidation stresses, 400, 600 and 800 Pa.

2.2.4.5. Solid state characterization

The polymorphic mannitol composition in the spray dried and coprocessed samples was analyzed using Raman spectroscopy, X-ray diffraction (XRD) and modulated differential scanning calorimetry (MDSC).

Raman spectra (Raman Rxn1, Kaiser Optical Systems, Ann Arbor, United States) of the samples were recorded (n=8) using exposure times of 10 s with 3

accumulations. All spectra were recorded with a resolution of 4 cm^{-1}. The spectral region between 1000 and 1200 cm^{-1} was selected for evaluation of mannitol polymorphism. Spectra were centered and SNV-correction was applied to correct for the physical variation between measurements. The spectra were used for identification of the polymorphic forms present in the formulation and therefore the spectra were compared with the spectra of reference material of α-, β- and δ-mannitol. Additionally, principal component analysis (PCA) was executed on the spectra of the pilot-scale spray dried samples with Simca 13.0.3 software (Umetrics, Umeå, Sweden). To investigate the stability of the pilot-scale spray dried samples, they were stored 6 months at 60% relative humidity and 25 °C and reanalyzed by Raman spectroscopy as described above.

XRD analysis of the samples and mannitol references was performed on a CuKα diffractor (ARL™ X'TRA, Thermo Fischer Scientific, Waltham, United States) with a voltage of 40 mV in the angular range of $5°<2\theta<60°$ using a step scan mode with step size of 0.02° and counting time of 1s/step.

MDSC was performed using a Q2000 differential scanning calorimeter (TA Instruments, Zellik, Belgium) equipped with a refrigerated cooling system. Samples (5–10 mg) were accurately weighed and run in Tzero pans (TA Instruments, Zellik, Belgium). They were cooled to -20 °C and subsequently heated up to 220 °C with a heating rate of 2 °C/min. The modulation time and amplitude were set at 60 s and 0.318 °C, respectively. Dry nitrogen was used as a purge gas through the cell at a flow rate of 50 ml/min. The results were analyzed using TA Instruments Universal Analysis software.

2.2.5. Tablet characterization

The hardness, thickness and diameter of the tablets (n=10) were determined using a hardness tester (Type HT 10, Sotax, Basel, Switzerland) and the tensile strength (TS) of the tablets was calculated according to the formula of Fell and Newton [15]:

$$TS = 2F/\pi dt$$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

The friability of tablets compressed at 184 (±5) MPa was determined using a friabilator (PTFE, Pharma Test, Hainburg, Germany) as described in the European

Pharmacopea at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

3. Results and discussion

3.1. Influence of PVP inclusion and outlet temperature on the formation of δ-mannitol

In preliminary experiments spray dried mannitol samples without PVP (F1) and with 20% PVP (F3) were prepared on a lab-scale spray dryer. Identification of the mannitol polymorphs in the samples was performed by Raman spectroscopy, XRD and MDSC through comparison with reference material of α-, β- and δ-mannitol. Raman spectroscopy (Figure 1) and XRD (Figure 2) identified a mixture of α- and β-mannitol in the sample without PVP and δ-mannitol the sample with 20% PVP, respectively. MDSC analysis of the samples proved not to be helpful for the identification of different mannitol polymorphs since a melting peak at 166 – 167 °C with identical melting enthalpy was detected for reference material of α-, β- and δ-mannitol. Not uniform melting of δ-mannitol at 155 °C followed by crystallisation to α- or β-mannitol and melting of the respective crystal form or mixture is nevertheless reported in literature [8, 16].

Formulations F1-3 (Table 1), containing different PVP concentrations in the final spray dried powder, were spray dried on a pilot-scale spray dryer at 2 different outlet temperatures (To): 60 and 80 °C. The influence of the PVP content and the outlet temperature on the mannitol polymorph formed during spray drying was qualitatively evaluated by Raman spectroscopy. The results of the Raman analysis were summarized in a PC1 versus PC2 scores plot of the first and second principal component (PC), explaining 83% and 15% of the variation in the dataset, respectively (Figure 3). Analysis of the loading plots (Figure 4) of the PC learned that the first PC was selective for the presence of δ-mannitol whereas the second PC could differentiate between α- and β-mannitol. Three clusters of samples around the data points of the α-, β- and δ-mannitol reference materials could be differentiated on the PC1 versus PC2 scores plot. Independently of the applied outlet temperature, the spray dried samples containing 0% and 10% PVP consisted of exclusively β- and α-mannitol, respectively. Inclusion of 20% PVP in the formulation (F3) yielded powders consisting of mainly δ-mannitol but traces of α-mannitol were also detected. The polymorphic content in these samples was dependent on the outlet temperature used. Applying an outlet temperature of 60 °C resulted in a spray

dried sample with exclusively δ-mannitol next to PVP whereas traces of α-mannitol were still present in the sample spray dried at an outlet temperature of 80 °C. These results were confirmed by XRD (Figure 5) as characteristic peaks of β-mannitol (10.56°, 14.71°), α-mannitol (13.79°) and δ-mannitol (9.57°) were detected in samples F1, F2 and F3, respectively. [5, 6, 7, 8, 17, 18].

The yields of the spray drying experiments and residual moisture content of the resulting samples are listed in Table 3. The process yield varied between 23 and 89%, depending on the percentage of PVP in the formulation and the outlet temperature used. Inclusion of PVP decreased the process yield due to the sticky nature of PVP and its high hygroscopicity which is also reflected in the high residual moisture content of the samples with 20% PVP [4]. Increasing the outlet temperature positively influenced the yield as the particles were drier and therefore less sticky before they hit the dryer wall.

Spray drying of a pure mannitol solution resulted in small agglomerates composed of spherical particles (Figure 6). Addition of PVP to the spray dried mannitol solution yielded larger coalesced particles where individual particles were more difficult to distinguish.

The particle size distribution and median particle size (d_{50}) of spray dried samples F1-3 is shown in Figure 7. Inclusion of PVP in the formulation resulted in particles with a higher d_{50} value since PVP acted as a binder favoring agglomeration during the spray drying process. However, increasing the PVP content from 10 to 20% in the final spray dried samples had no effect on d_{50}. The larger d_{50} of F2 and F3 was reflected in their flowability as they were classified as easy-flowing (despite the higher moisture content of these samples), whereas F1 was classified as very cohesive based on the ffc values. Thus, inclusion of PVP in the formulation to form δ-mannitol during spray drying also proved to be an asset with regard to flowability.

Compression profiles of the spray dried samples were constructed for evaluation of the tabletability of the different mannitol polymorphs (Figure 8, full lines). The spray dried sample with δ-mannitol (F3) clearly exhibited superior tabletability in comparison to the samples with the α- and β-polymorphs (F1, F2), reaching a maximum TS of 6.2 (±0.3) MPa at a main compression pressure (MCP) of 184 (±5) MPa. Note that the PVP content of these samples was different. To exclude the effect (a plastically deforming binder under compression) paracetamol formulations containing the different spray dried mannitol samples with a constant (5%) PVP content (PM1-3 in Table 2) were processed into tablets (depending on the formulation part of PVP was included in the spray dried material and/or added as such to the physical mixture). Their tabletability is also included in Figure 8 (dotted

lines). Obviously the tabletability of these formulations is lower compared to the spray dried samples due to the high load (75%) of paracetamol, a model drug known for its poor tabletability. However, the tabletability of the formulation containing δ-mannitol (PM3) was significantly higher than of the physical mixtures with α- and β-mannitol (PM1 and PM2), which was linked to the superior tabletability of δ-mannitol. This confirmed the findings of Burger et al. and Wagner et al. [3, 8].

The excellent tabletability of spray dried δ-mannitol and PVP was also reflected in the friability of the tablets. While the friability of tablets composed of spray dried samples was below 0.1% (independently of their polymorphic content or the percentage PVP), the inclusion of paracetamol in the physical mixtures resulted in a friability of 6.4%, 6.4% and 3.0% for PM1, 2 and 3, respectively.

3.2. Tabletability of coprocessed samples

Since production of δ-mannitol in a continuous way via spray drying was possible, it was next investigated whether paracetamol and δ-mannitol could be coprocessed in a single step, using the method proposed by Vanhoorne et al. [14]. Paracetamol crystals were injected into a spray of atomized drops during the spray drying process. An aqueous solution of 18.0% w/w mannitol (F4) and an aqueous solution of mannitol and PVP (F5) were spray dried (Table 2). The ratio of mannitol to PVP in F5 was 4:1 which is equal to the ratio used in the spray drying experiments (F3) yielding δ-mannitol.

The polymorphic state of mannitol in the coprocessed samples was investigated by XRD and Raman spectroscopy. Identification of the mannitol polymorphs by XRD was not possible due to the presence of 75% paracetamol, dominating the spectrum. Raman analysis revealed the presence of β-mannitol in coprocessed sample F4. However, δ-mannitol could not be detected in coprocessed sample F5 via Raman spectroscopy due to the dominant influence of paracetamol on the spectrum. Since it was proven in the first part of the study that spray drying mannitol and PVP in a ratio of 4:1 yielded δ-mannitol on both a lab scale and pilot scale spray dryer irrespectively of the applied outlet temperature, the presence of δ-mannitol in sample F5 was assumed.

The morphology of the coprocessed samples was evaluated by SEM and is shown in Figure 9. In this case no spherical particles were obtained since irregular-shaped paracetamol crystals were introduced in the spray of atomized drops, and their shape dominated in the collected spray dried powder. More agglomerated particles were observed in sample F5 which was attributed to PVP acting as a

binder. This was confirmed by laser diffraction analysis of the samples (Figure 10): d_{50} of samples F4 and F5 were 108.2 µm and 230.9 µm, respectively, exceeding the d_{50} of paracetamol starting material (44.4 µm). Thus in both experiments agglomeration occurred, however, inclusion of PVP in F5 favored agglomeration. Despite the significant difference in particle size of the coprocessed samples, both were classified as cohesive based on their ffc value (which is linked to their irregular shape).

The tabletability of the coprocessed samples (F4 and F5) was compared to the tabletability of physical mixtures (PM3 and PM4) with the same composition (Figure 11). The tabletability of coprocessed sample F4 was slightly but significantly better than of its physical mixture PM4. In contrast, the tabletability of coprocessed sample F5 was clearly superior to the tabletability of physical mixture PM3: the TS of PM3 tablets was 0.9 MPa at a MCP of 300 MPa, whereas F5 tablets yielded a TS of 2.1 MPa. This demonstrated the added value of the applied coprocessing method which is due to the coating of paracetamol crystals with δ-mannitol and PVP.

While the tablet friability of coprocessed sample F4 (30.5%) and the corresponding physical mixture PM4 (46.8%), which contained 25% β-mannitol and 75% paracetamol, was too high, the friability of the coprocessed sample F5, formulated with 5% PVP, 20% δ-mannitol and 5% paracetamol was excellent (0.5%) and considerably lower than of the corresponding physical mixture PM3 (3.0%) which again illustrated the added value of the coprocessing method.

3.3. Stability of the spray dried samples

It is well known that thermodynamically unstable polymorphs can convert over time to a more stable crystal form. As the δ-polymorph is not the thermodynamically stable crystal form of mannitol at ambient conditions, the physical stability of the spray dried samples (F1-3) stored at 60% relative humidity and 25 °C during 6 months was investigated by Raman spectroscopy [8]. No spectral differences were detected after storage which indicated stability of all mannitol polymorphs over at least 6 months. Kinetic stability of α- and δ-mannitol was also proven by Burger et al. during mechanical stress and storage for over five years at 25 °C at a relative humidity of 43% [8].

4. Conclusions

Spray drying an aqueous solution of mannitol and PVP (mannitol:PVP: 4:1) resulted in formation of δ-mannitol which exhibited excellent tabletability and friability in comparison to α- and β-mannitol. Inclusion of PVP in the spray dried mannitol solution positively influenced the flowability since the resulting agglomerates were larger.

Additionally, a coprocessing method was applied for the production of δ-mannitol in a continuous way by spray drying aqueous solutions of mannitol and PVP and to agglomerate these particles with paracetamol crystals in the same process. The tabletability and friability of the resulting particles was excellent which was attributed to the superior tabletability of δ-mannitol over α- and β-mannitol and to the application of the coprocessing method which enabled coating of paracetamol crystals with δ-mannitol and PVP.

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Tables

Table 1: Overview of the spray dried solutions and composition of the final spray dried and coprocessed samples.

	Composition of spray dried solutions (% w/w)		**Feed rate solid particle introduction (g/min)**	**Final composition of spray dried sample (% w/w)**			**Spray dryer**
	PVP	**mannitol**		**PVP**	**mannitol**	**paracetamol**	
F1	0	18.0	-	0	100	-	lab-scale + pilot-plant
F2	1.8	16.2	-	10	90	-	pilot-plant
F3	3.6	14.4	-	20	80	-	lab-scale + pilot-plant
F4	0	16.0	48	0	25	75	production-scale
F5	3.2	12.8	48	5	20	75	production-scale

Table 2: Overview of the prepared physical mixtures.

	SD sample (% w/w)	Paracetamol (% w/w)	PVP (% w/w)
PM1	20.0 (F1)	75.0	5.0
PM2	22.5 (F2)	75.0	2.5
PM3	25.0 (F3)	75.0	-
PM4	25.0 (F1)	75.0	-

Table 3 Overview of the yield and residual moisture (±SD) content of the spray drying experiments performed on the pilot-scale spray dryer.

Outlet temperature (°C)	**Formulation**	**Yield (%)**	**Moisture content (%)**
60	F1	70	0.16 (± 0.05)
	F2	54	3.10 (± 0.10)
	F3	23	5.50 (± 0.10)
80	F1	89	0.63 (± 0.07)
	F2	66	2.56 (± 0.09)
	F3	59	5.19 (± 0.10)

Figures

Figure 11 Tabletability of coprocessed samples F4 and F5 and corresponding physical mixtures PM4 and PM3.

Figure 1 Raman spectra of α-, β- and δ-mannitol reference material and samples F1 and F3 spray dried on a lab-scale spray dryer.

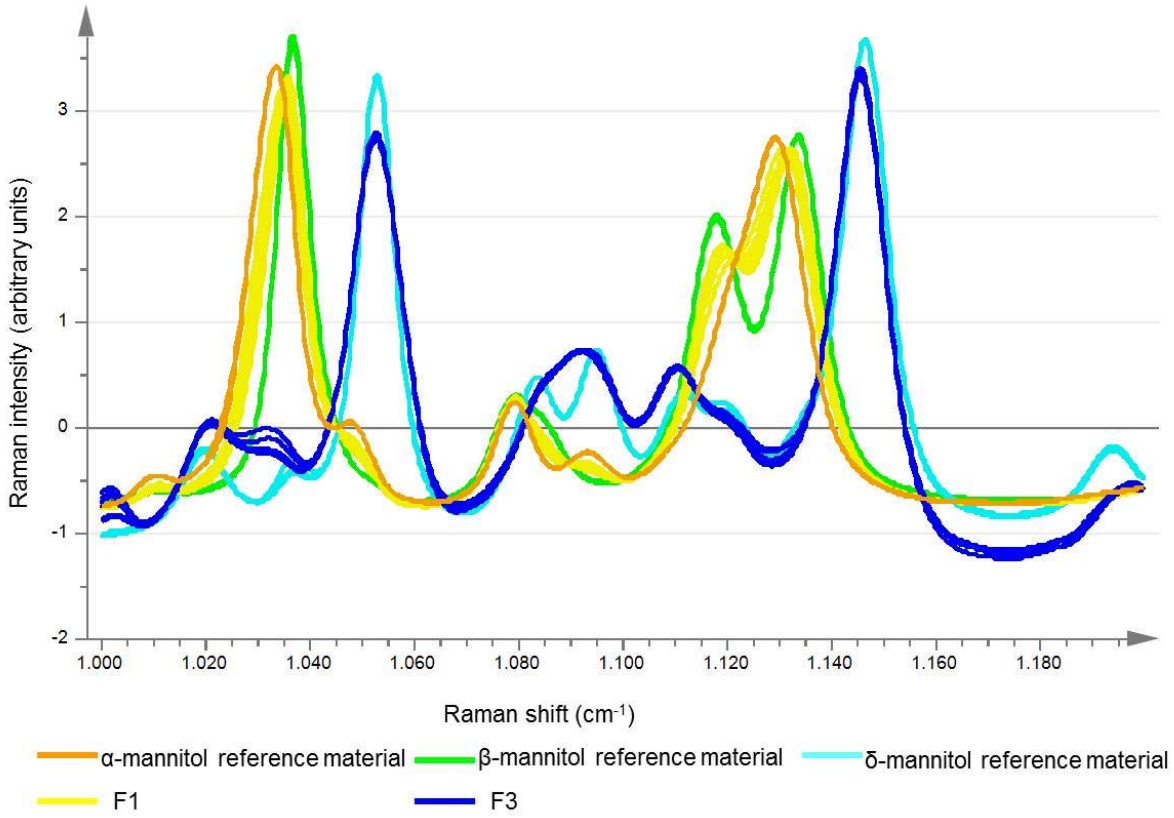


Figure 2 XRD spectra of α-, β- and δ-mannitol reference material and samples F1 and F3 spray dried on a lab-scale spray dryer.

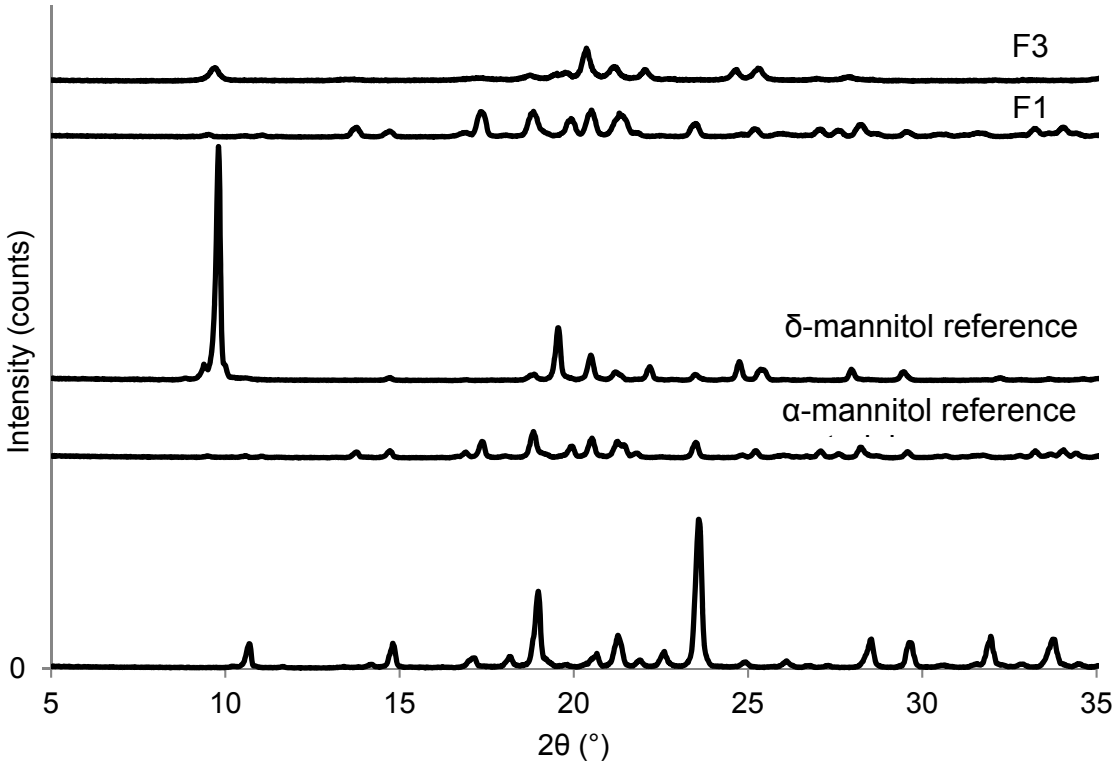


Figure 3 PC1 versus PC2 scores plot obtained after PCA of all pilot-scale spray dried samples (To 60 °C and 80 °C) and reference material of α-, β- and δ-mannitol.

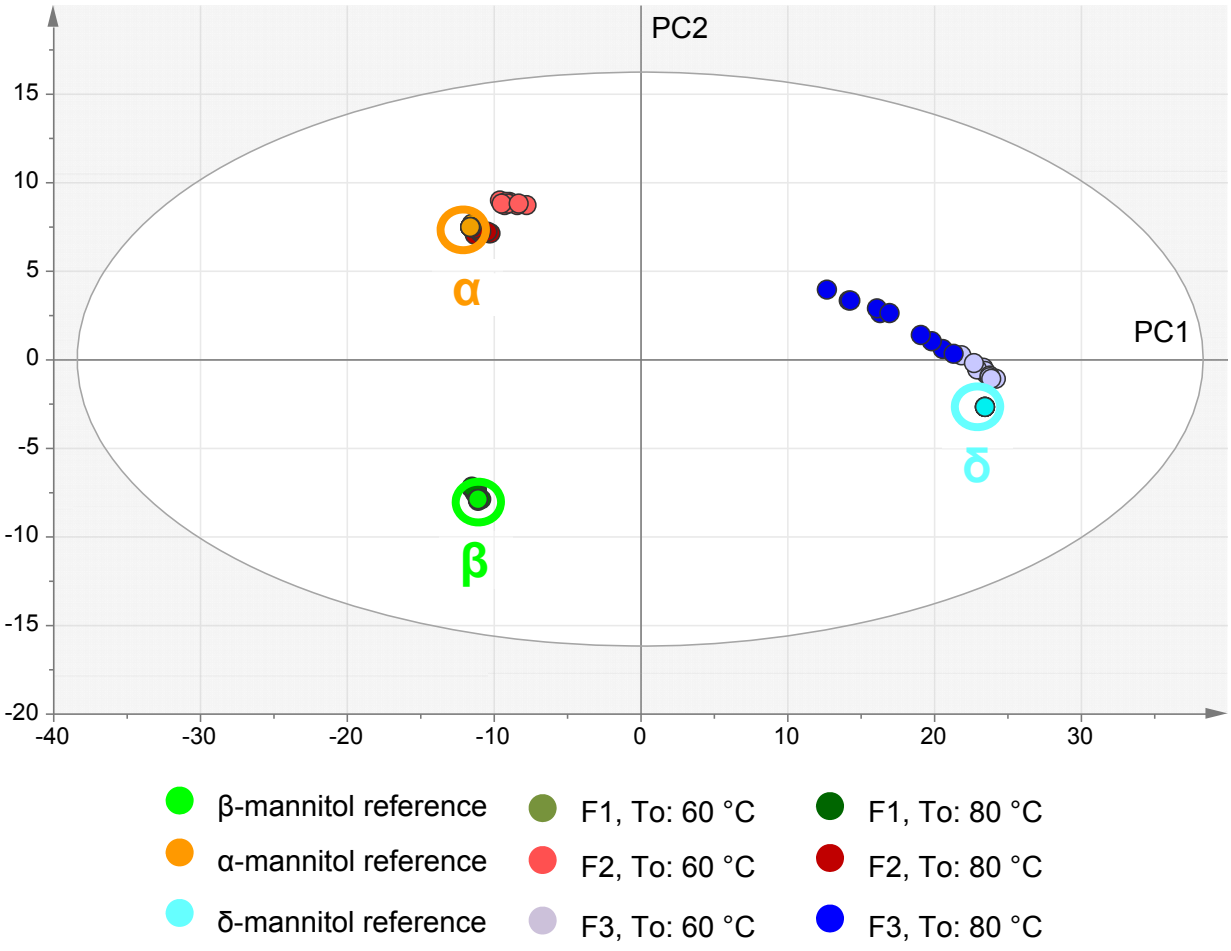


Figure 4 Raman spectra of α-, β- and δ-mannitol reference material and loadings of PC1 and PC2 obtained after PCA analysis.

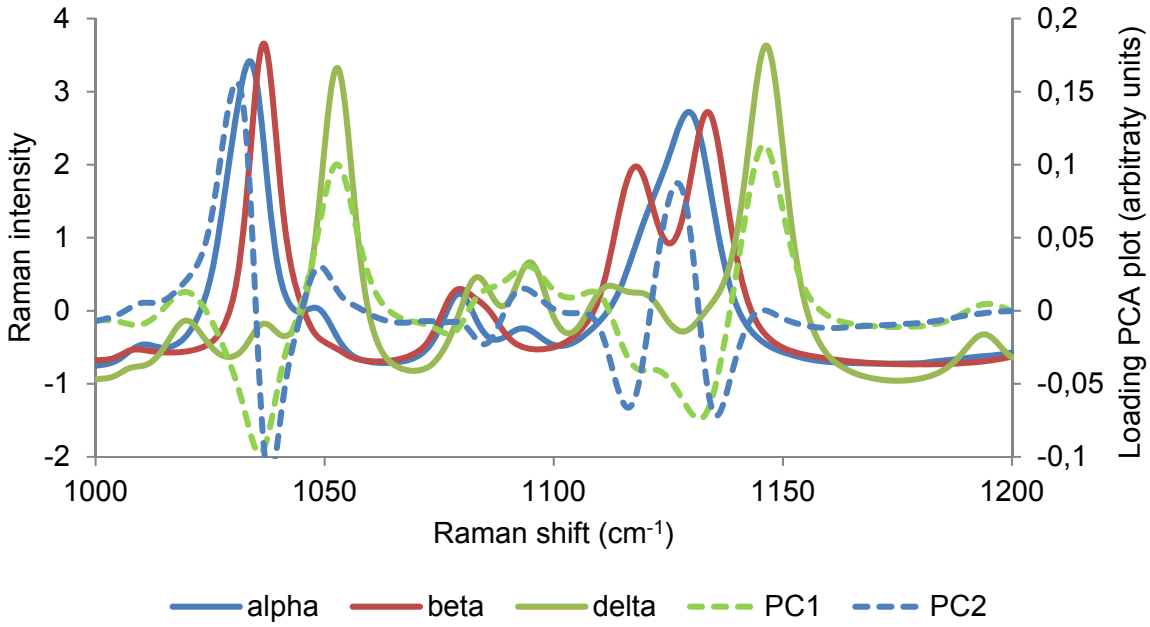


Figure 5 XRD patterns of α-, β- and δ-mannitol reference material and samples F1-3 spray dried at To 80 °C and 60 °C.

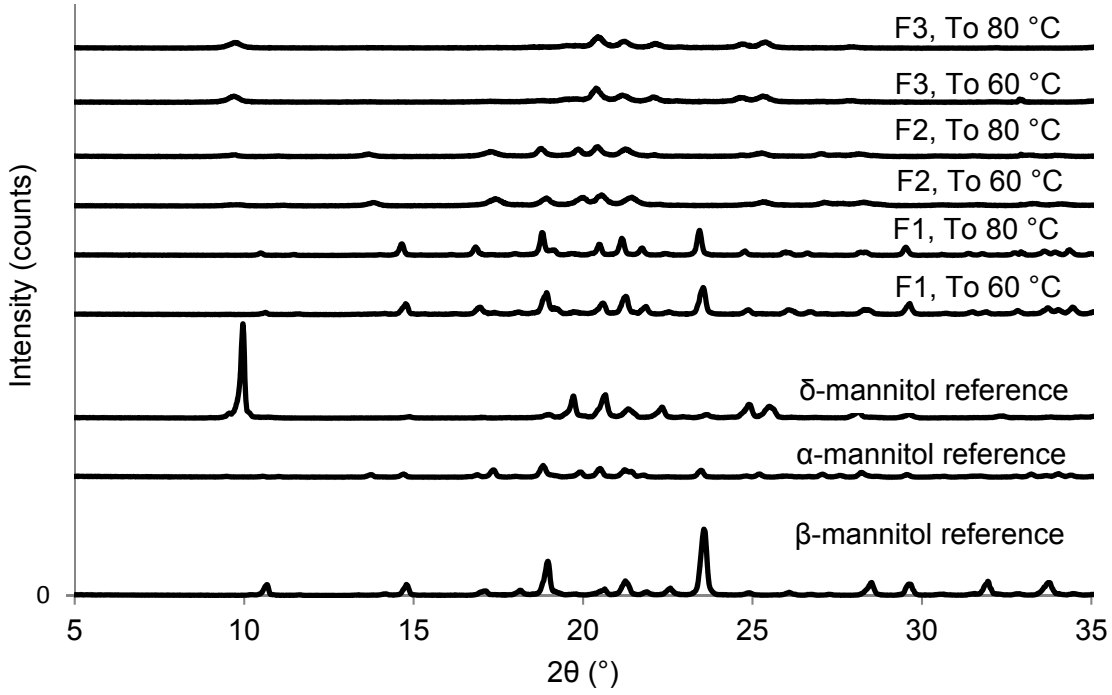


Figure 6 SEM images of spray dried samples F1-3.

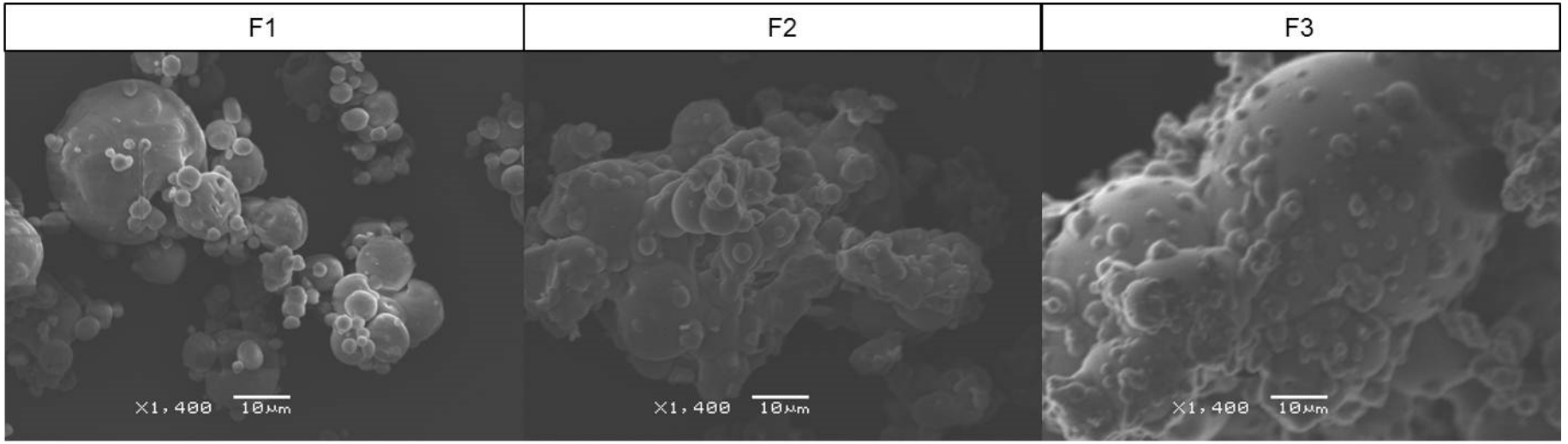


Figure 7 Particle size distribution of samples F1, F2 and F3 spray dried at an outlet temperature of 80°C.

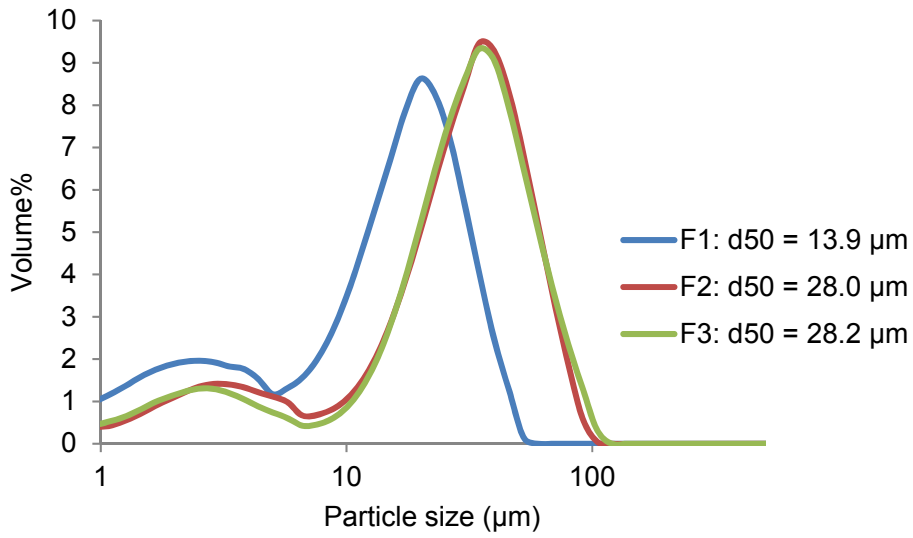


Figure 8 Tabletability of the spray dried powders (F1-3) and physical mixtures (PM1-3).

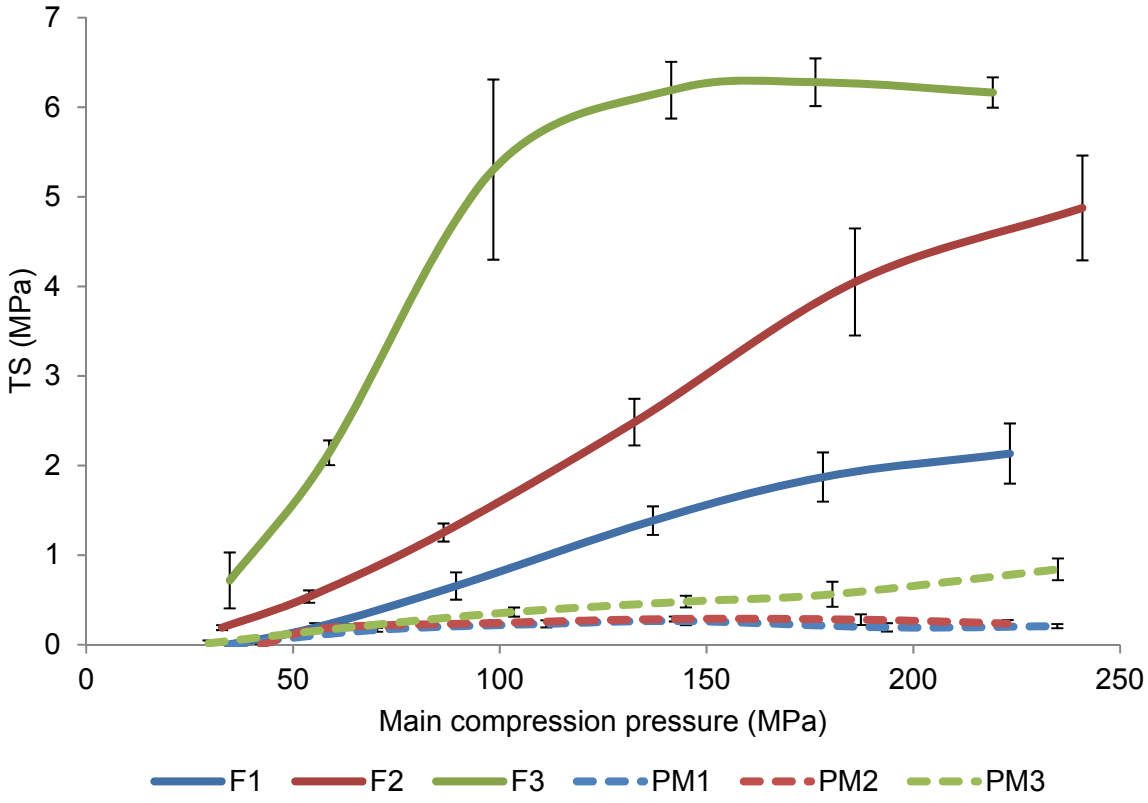


Figure 9 SEM images of coprocessed samples F4 and F5.

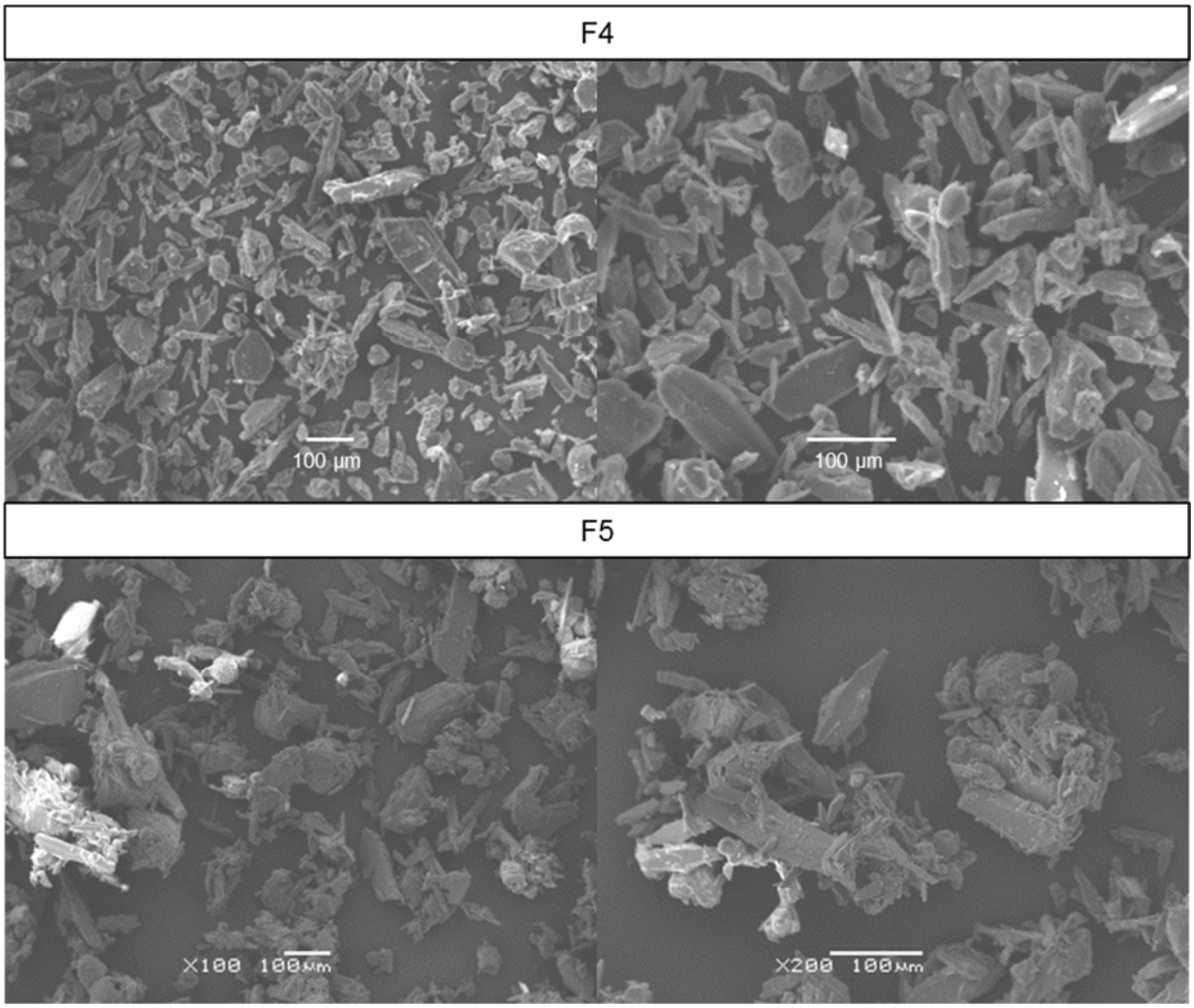
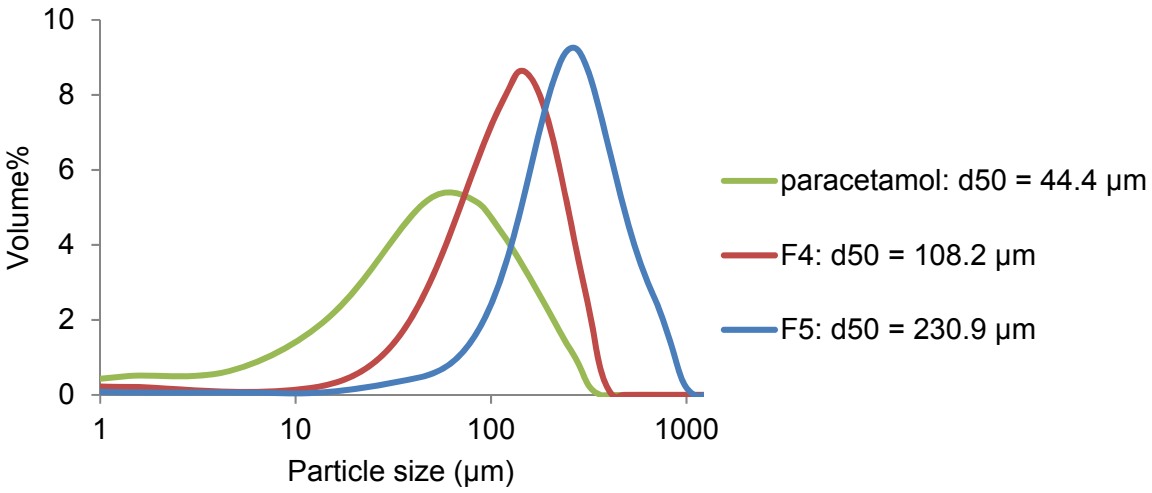


Figure 10 Particle size distribution of paracetamol starting material and coprocessed samples F4 and F5.


10
8
6
4
2
0
Volume%
1
10
100
1000
Particle size (µm)
paracetamol: d50 = 44.4 µm
F4: d50 = 108.2 µm
F5: d50 = 230.9 µm

5

Figure 11 Tabletability of coprocessed samples F4 and F5 and corresponding physical mixtures PM4 and PM3.